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DRUPANGTONINE, A NOVEL ANTILEUKEMIC ALKALOID FROM *CEPHALOTAXUS HARRINGTONIA* VAR. *DRUPACEA*

Ichiro Takano,*[a] Ichiro Yasuda,[a] Motohiro Nishijima,[a]
Yukio Hitotsuyanagi,[b] Koichi Takeya[b] and Hideji Itokawa[b]

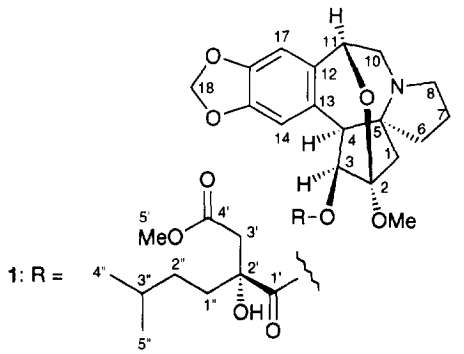
[a] *The Tokyo Metropolitan Research Laboratory of Public Health, Hyakunin-cho, Shinjyuku-ku, Tokyo 169, Japan*

[b] *Tokyo University of Pharmacy and Life Science, Horinouci, Hachioji, Tokyo 192-03, Japan*

Abstract: Drupangtonine (**1**), a novel *Cephalotaxus* alkaloid, has been isolated from *Cephalotaxus harringtonia* var. *drupacea*, and its structure has been elucidated based on spectroscopic analyses. Compound **1** strongly inhibits the growth of P-388 leukemia cells. Copyright © 1996 Elsevier Science Ltd

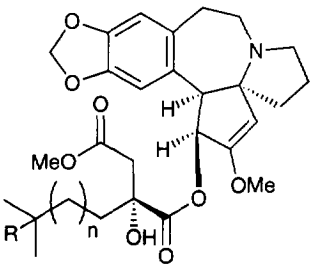
The ester-type *Cephalotaxus* alkaloids were isolated from *Cephalotaxus* spp., and their unique structure and potent antileukemic activities have drawn the attention of many chemists.[1] Our recent effort to search for potent antileukemic substances in *Cephalotaxus harringtonia* var. *drupacea* has resulted in the isolation of a novel oxygenated ester-type alkaloid **1**, designated drupangtonine. In this communication, we wish to report the structure of this new alkaloid and the antileukemic activity against P-388 leukemia cells.

Drupangtonine (**1**)[2] had the molecular formula $C_{28}H_{37}NO_9$ that was established by high-resolution FABMS, indicating eleven degrees of unsaturation. The spectral data of **1** revealed the presence of a hydroxyl group (3500 cm^{-1}), two methoxyl groups (δ_H 3.40, δ_C 51.7 and δ_H 3.66, δ_C 51.7), an aromatic ring with two para coupling protons (δ_H 6.45, δ_C 111.0 and δ_H 6.65, δ_C 107.6), a methylenedioxy group (δ_H 5.86, 5.91; δ_C 101.0) and two AB type methylenes (δ_H 1.54, 2.68; δ_C 35.9 and δ_H 1.97, 2.32; δ_C 42.5). Furthermore, the X position of the signal of an ABX system (δ_H 4.85; δ_C 78.1) assignable to C-11 which was on a carbon bearing both oxygen and aryl functions was observed. These spectral data were very similar to those of drupacine (**2**).[3,4] Thereby **1** turns out to be partly made of a drupacine-like framework. In addition, two ester carbonyl groups (δ_C 170.9, 174.1) and two terminal methyl groups (δ_H 0.82, 0.83; δ_C 22.4, 22.5) indicated that **1** had an ester-type side chain moiety at the C-3 position. Taking its drupacine-type cyclic system and side chain moiety in consideration, HMBC[5] correlations between the proton signals of the above structural fragments and nine quaternary carbon signals including the sp^3 carbons at δ_C 65.8, 74.8, 107.6, 130.4, 131.6, 145.9, 146.9, 170.9 and 174.1 could assemble the planar structure. The NOESY correlations of 1-H$_\alpha$ with 3-H; 1-H$_\beta$ with 8-H$_\beta$ and 10-H$_\beta$; 4-H with 6-H$_\alpha$ and 14-H; 8-H$_\alpha$ with 10-H$_\alpha$; and 11-H with 17-H set up the molecular models which disclosed the ring formation as shown in structure **1**. This structure is rigidified through the ether linkage between C-2 to C-11 on the β face of the molecule and well explains the vicinal coupling constants of 11-H with



1: R =

2: R = H



3: R = OH, n = 1
4: R = OH, n = 2
5: R = H, n = 1

10-H$_\alpha$ (J = 4.5 Hz) and 10-H$_\beta$ (J = 0 Hz). The CD spectrum of **1** showed Cotton effects ([θ]$_{286}$ +3500, [θ]$_{264}$ 0, [θ]$_{248}$ −7500, [θ]$_{228}$ 0, [θ]$_{215}$ +9000) similar to those of drupacine.[6] Furthermore, the CD spectrum for the molybdate complex of a diacid moiety derived from the acid hydrolysis of **1** showed a negative Cotton effect ([θ]$_{275}$ −6900).[7] Therefore, the absolute stereochemistry of **1** was established as 3*S*, 4*S*, 5*R*,11*R* and 2'*R*.

The IC$_{50}$ value of **1** against P-388 leukemia cells was 0.0070 μg/mL, and it is stronger than those of harringtonine (**3**, 0.032 μg/mL)[8] and homoharringtonine (**4**, 0.017 μg/mL),[8] and as strong as that of deoxyharringtonine (**5**, 0.0075 μg/mL).[8] The fact that the alkaloid **1** possessing a drupacine-type rigid structure showed potent activity will provide valuable information for the identification of the active conformation of this type of alkaloid.

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References and notes

1. Huang, L.; Xue, Z. In *The Alkaloids*; Brossi, A., Ed.; Academic: Orlando, 1984; Vol. 23, pp 157–226.
2. 1.2 mg of **1** was isolated from 1.5 kg of the MeOH extract of the plant. Oil, [α]$_D$ −24° (*c* 0.06, MeOH); HR-FABMS *m/z* 532.2564 [M+H]$^+$ (Calcd for $C_{28}H_{38}NO_9$: 532.2547); λ_{max} (MeOH) nm: 291 (log ε 3.48); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 6.2 Hz, 4"-Me), 0.83 (3H, d, J = 6.2 Hz, 5"-Me), 0.98 (1H, m, 2"-H$_a$), 1.24 (1H, m, 2"-H$_b$), 1.43 (3H, m, 1"-H$_a$, 1"-H$_b$ and 3"-H), 1.54 (1H, d, J = 14.0 Hz, 1-H$_\alpha$), 1.77 (2H, m, 7-H), 1.97 (1H, d, J = 16.3 Hz, 3'-H$_a$), 2.05 (1H, ddd, J = 12.8, 8.6, 5.8 Hz, 6-H$_\beta$), 2.20 (1H, ddd, J = 12.8, 9.5, 7.2 Hz, 6-H$_\alpha$), 2.32 (1H, d, J = 16.3 Hz, 3'-H$_b$), 2.43 (1H, ddd, J = 9.5, 9.5, 9.5 Hz, 8-H$_\beta$), 2.68 (1H, d, J = 14.0 Hz, 1-H$_\beta$), 2.98 (1H, br-d, J = 13.0 Hz, 10-H$_\beta$), 3.08 (1H, ddd, J = 9.5, 7.8, 3.9 Hz, 8-H$_\alpha$), 3.11 (1H, dd, J = 13.0, 4.5 Hz, 10-H$_\alpha$), 3.40 (3H, s, 19-Me), 3.59 (1H, d, J = 9.6 Hz, 4-H), 3.66 (3H, s, 5'-Me), 4.85 (1H, d, J = 4.5 Hz, 11-H), 5.16 (1H, d, J = 9.6 Hz, 3-H), 5.86 (1H, d, J = 1.5 Hz, 18-H$_a$), 5.91 (1H, d, J = 1.5 Hz, 18-H$_b$), 6.45 (1H, s, 14-H), 6.65 (1H, s, 17-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3 (t, C-7), 22.4 (q, C-4"), 22.5 (q, C-5"), 28.0 (d, C-3"), 31.5 (t, C-2"), 35.9 (t, C-1), 36.8 (t, C-1"), 42.5 (t, C-3'), 43.3 (t, C-6), 51.7 (q, C-19), 51.7 (q, C-5'), 54.0 (t, C-8), 56.9 (t, C-10), 57.0 (d, C-4), 65.8 (s, C-5), 74.4 (d, C-3), 74.8 (s, C-2'), 78.1 (d, C-11), 101.0 (t, C-18), 107.6 (d, C-17), 107.6 (s, C-2), 111.0 (d, C-14), 130.4 (s, C-13), 131.6 (s, C-12), 145.9 (s, C-15), 146.9 (s, C-16), 170.9 (s, C-4'), 174.1 (s, C-1').
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8. The values were obtained by the comparative experiments with compound **1**.

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